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Anaemia, acute renal failure and proteinuria – A case to solve

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CLINICAL PRESENTATION

A 70-year-old man was admitted to our hospital emergency for epigastralgy and haematemesis. He had a past history of: controlled long-time hypertension, gastric ulcer complicated with perforation two years before and osteo-articular pain with daily intake of paracetamol and metamizole. He denied NSAIDs intake and family history of renal disease.

His chronic medication was: furosemide 40 mg/day, ramipril/hydrochlorothiazide 5 mg + 25 mg/day, amlodipine 5 mg/day, allopurinol 300 mg/day and pantoprazole 20 mg/day.

The initial analytic study revealed normocytic normochromic anaemia (haemoglobin 8.1 g/dl), acute renal failure (creatinine 6.48 mg/dl and urea 234 mg/dl).The 24-hours proteinuria was 787 mg. Serum C3 level was slightly low and serum C4 level was normal. Antinuclear antibodies (ANA), cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA), proteinase 3 anti-neutrophil cytoplasmic antibodies (PR3-ANCA) and anti-glomerular basement membrane antibodies (anti- GBM) were negative. Serology for hepatitis B, hepatitis C and HIV were negative.

KIDNEY HISTOLOGY

Figure 1 shows nodular expansions of mesangial matrix without mesangial hypercellularity witch represent nodular sclerosing glomerulopathy. The nodules stain by periodic acid-shift (PAS). In this figure the thickening of tubular and vessel basement membranes which are PAS positive can also be seen.

In **Figure 2**, glomerular nodules are present but negative or weakly positive for silver stain.

The Masson's trichrome (MT) in **Figure 3** shows an area of interstitial fibro-oedema associated to acute tubular necrosis. The majority of tubulointerstitial parenchyma is preserved. The visible glomerular nodules are MT positive.

Figure 4 shows immunofluorescence performed in frozen tissue. The staining of glomerular, tubular and

Figure 1
Periodic acid-shift; X 400

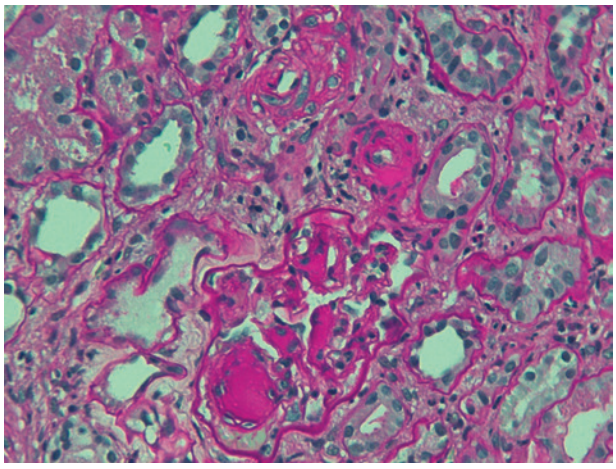


Figure 2

Methenamine Silver; X400

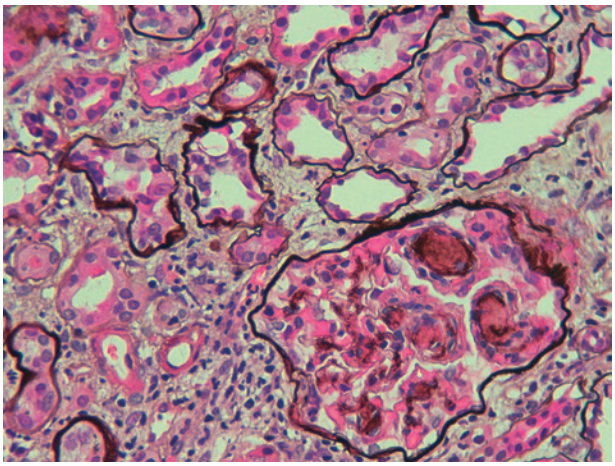


Figure 3

Masson's Trichrome; X200

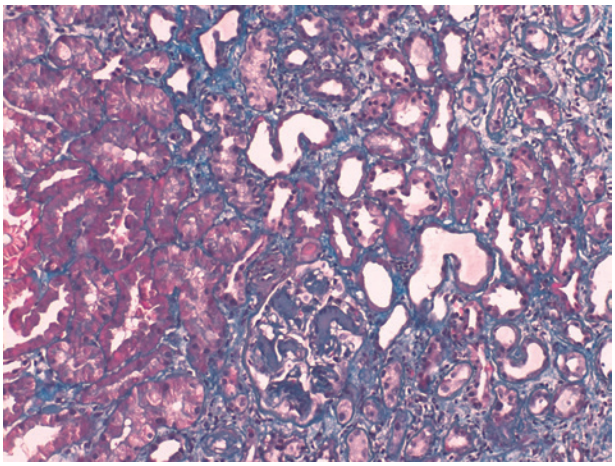
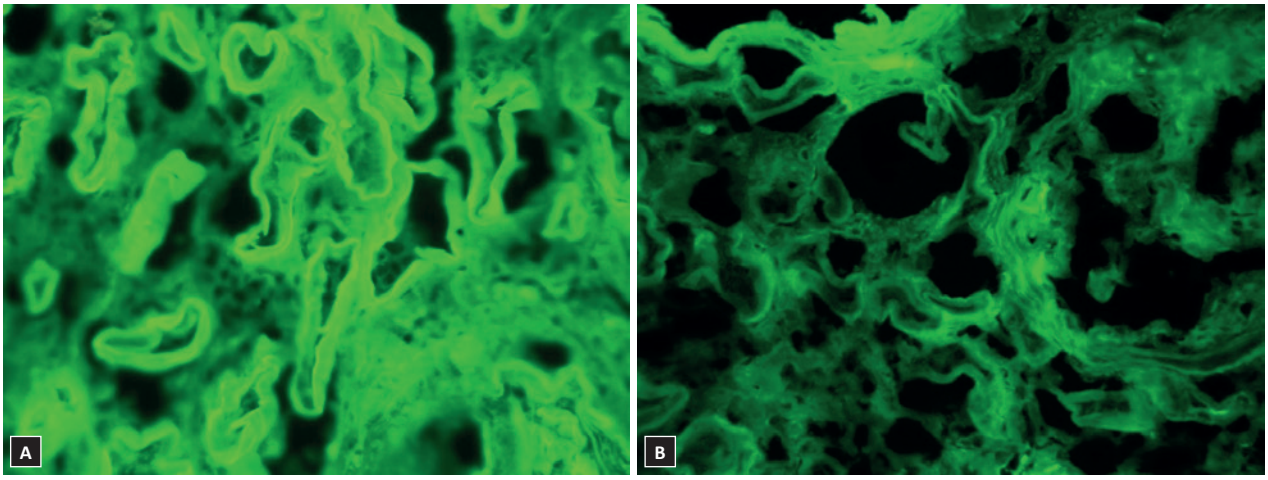


Figure 4

A – Immunofluorescence in frozen tissue – Kappa light chain; B – Immunofluorescence in frozen tissue – Lambda light chain



vascular basement membrane for kappa light chain is marked. Staining for lambda light chain is negative.

The remaining routine immunofluorescence is negative. No birefringence of Congo red under polarization was found.

COMPLEMENTARY STUDY

The electrophoresis and immunofixation performed in serum and urine do not reveal monoclonal component. The serum-free kappa light chain was 567 mg/l (normal: 3.3-19.4 mg/l); serum-free lambda light chain was 42 mg/l (normal: 5.51-26.30 mg/ml). The ratio kappa/ lambda were 13.5 (reference in kidney failure: 0.37-3.1).

Myelogram and bone biopsy were performed after the kidney biopsy result. The myelogram revealed 16% of plasmocytes. The bone biopsy demonstrated that plasmocytes (CD138+/CD56+) were 10% of the total number of cells.

No osteolytic lesions were found by bone scintigraphy.

ANATOMO-CLINICAL DIAGNOSIS

Light-chain deposition disease associated to multiple myeloma

DISCUSSION

Monoclonal immunoglobulin deposition disease

Monoclonal immunoglobulin deposition disease (MIDD) is a systemic rare disease characterized by the deposition of nonamyloidotic monoclonal light- and/or heavy-chain deposits within basement membrane of glomeruli, tubules and vessels.[1]

Monoclonal immunoglobulin (MI) are secreted by a single clone of differentiated B cells that expand excessively either in a tumoural context (multiple myeloma) or without haematological neoplasm (monoclonal gammopathy of undetermined significance).The MI could be a free light chain or a heavy chain.[2]

MIDD is classified in three subtypes: in about 75% of cases as light-chain DD (LCDD); in about 11% of cases as light- and heavy-chain DD (LHCDD) and in about 14% of cases as heavy-chain DD (HCDD)[3]**.** In LCDD the monoclonal light chains are mainly of the kappa isotype (92%) and Gamma heavy chains predominate in HCDD**.**[1]

The kidney is almost always involved and the patients present with renal failure, proteinuria in association with dysproteinaemia. However, at the time of histological diagnosis of renal MIDD, up to 30% of patients have no detectable monoclonal protein in serum or urine. Even with use of the most sensitive techniques available, the percentage of patients falling into this category remain at 15% to 20%[4]**.**

About 60% of monoclonal immunoglobulin deposition disease (MIDD) presents as a nodular sclerosing glomerulopathy. In some cases, a membranoproliferative pattern can be seen. More rarely a necrotizing crescentic glomerulonephritis could be the histological manifestation of the disease.[5]

Nodular sclerosing glomerulopathy presents positive nodules in PAS and TM, negative or weakly positive nodules in silver stain and negative Congo red negative.[6]

Nodules of MIDD are uniform, generally affecting all the glomeruli relatively equally, with each glomerulus containing two or more nodules.[7]

Usually, the tubules show acute tubular injury. Concurrent cast nephropathy can be present in 30% of cases. The interstitium shows inflammation and oedema. A concentric thickening of small and medium vessel walls could be seen.[5,6,7]

The presence of a positive monotypic light and/or heavy chain makes the final diagnosis of MCDD.[5,6,7]

Monotypic light-chain deposits can be detected in glomerular and tubular basement membrane by immunohistochemistry in paraffin-embedded tissue.[5]

Immunofluorescence in frozen tissue allows monoclonal immunoglobulin staining.

The routine staining of renal biopsies for κ and λ light chains is imperative to identify unusual and early manifestations of these disorders.[6]

In electron microscopy, monoclonal immunoglobulin is seen as finely granular, punctuate, electron-dense deposits, along basement membranes. The deposits are similar in the 3 sub-types of MIDD.[5]

Differential diagnosis of nodular sclerosing glomerulopathy

Diabetic nephropathy

Glomeruloesclerosis in diabetic nephropathy mimics nodular sclerosing glomerulopathy. In diabetic nephropathy, the glomerular disease manifests initially as diffuse mesangial matrix expansion with or without mesangial hypercellularity. The diffuse mesangial sclerosis progress to a nodular pattern with disease evolution.[5,6,7]

Diabetic nephropathy is also characterized by exudative lesions, which consist of protein and some lipid. This lesions are highly eosinophilic globular structures overlying a capillary loop (fibrin cap) or along the inner aspect of Bowman's capsule (capsular drop).Capsular drop and hyaline cap lesions are not present in MIDD and are a clue in differential diagnosis.[7]

In diabetic nephropathy, immunofluorescence staining shows a characteristic linear staining of the glomerular and tubular basement membrane for

immunoglobulin G and albumin. Monotypic light- and/or heavy-chain deposition are not present.[5]

Amyloidosis

Glomerular amyloid appears as amorphous, acellular pink material in the mesangium and can also form mesangial nodules simulating MIDD or diabetic nephropathy.[7]

The amyloid deposits are negative in PAS stain, and have positive birefringence under light polarization on staining with Congo red stain.[5,6,7]

Idiopathic Nodular Glomerulopathy

Idiopathic Nodular glomerulopathy is defined by smoking and/or hypertension associated nodular glomeruloesclerosis in absence of diabetes mellitus. It is histologically characterized by rounded/nodular mesangial expansion that is PAS positive, silver stain and Congo red negative. Immunofluorescence is positive to IgM and C3 in sclerotic areas, presumably due to entrapment and not immune deposits.[5,6,7]

TREATMENT AND EVOLUTION

Twenty day after admission, haemodialysis was started for uraemic syndrome.

About one month after admission, the patient started treatment for multiple myeloma with bortezomib, cyclophosphamide and dexamethasone.

A significant decrease of serum free kappa light chain was rapidly observed after 3 months of therapy (from 567 to 44 mg/l) without kidney function recovery.

After 6 cycles of bortezomib, cyclophosphamide and dexamethasone, the patient is in remission of multiple myeloma but remains in haemodialysis.

Disclosure of Potential Conflicts of Interest: none declared

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